Pathophysiology and Genetics of Glycogen Storage Diseases

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Classical GSDs

- Glycogen storage diseases (GSDs) are a group of 19 hereditary diseases caused by a lack of one or more enzymes involved in the synthesis or degradation of glycogen and are characterized by deposits or abnormal types of glycogen in tissues.

The biochemistry at a glance

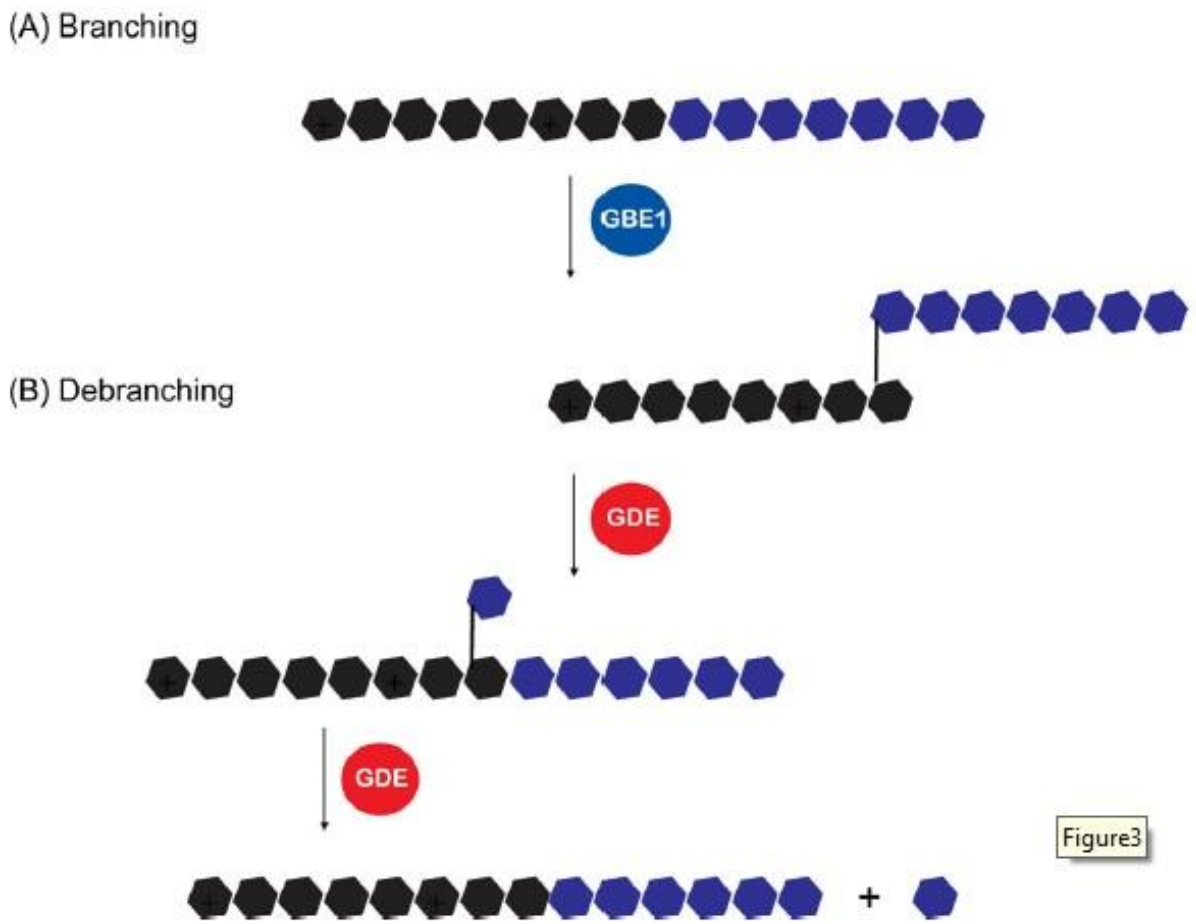
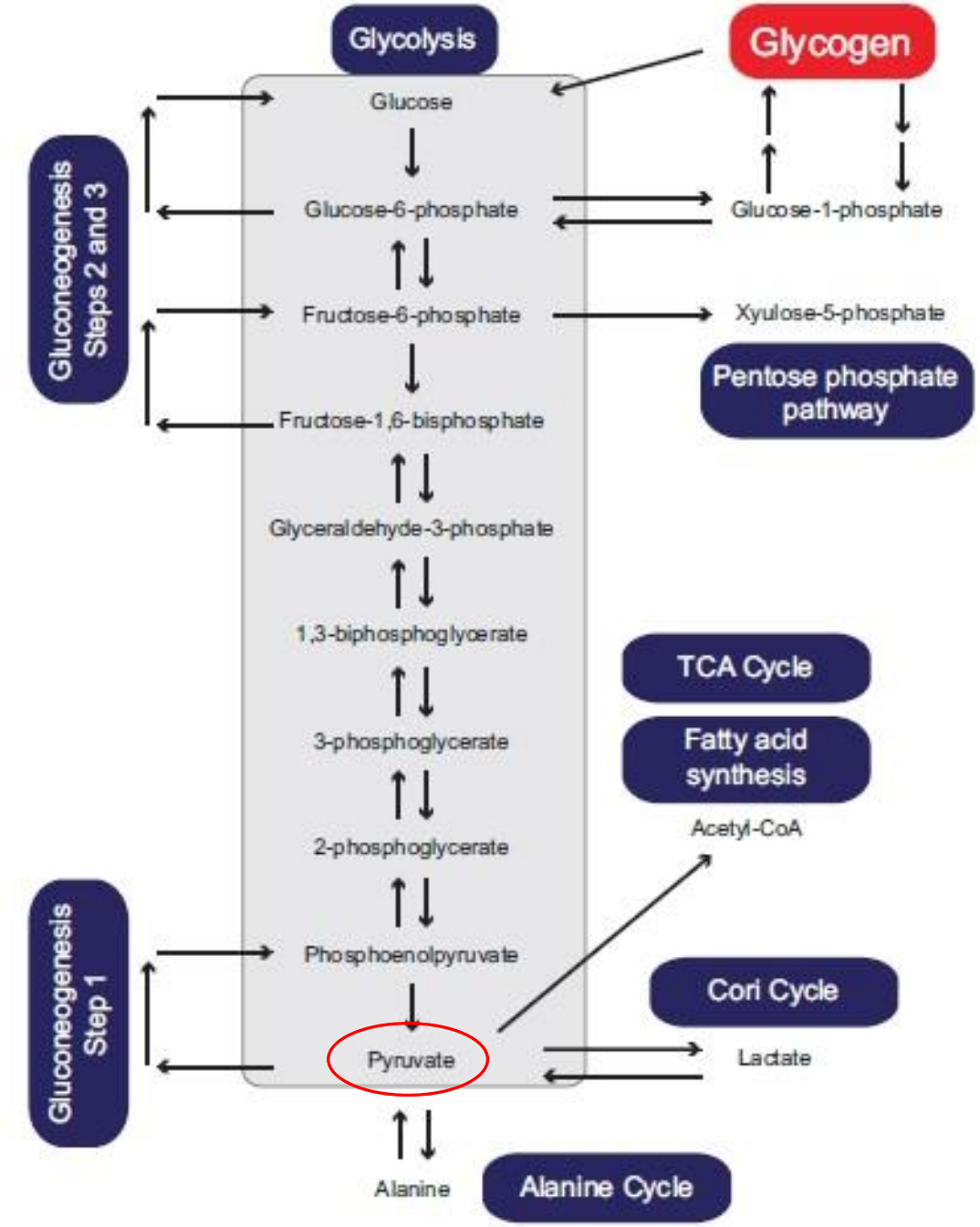


Figure3

Glycogen Degradation: Glycogenolysis



Glycogen Degradation: Glycophagy

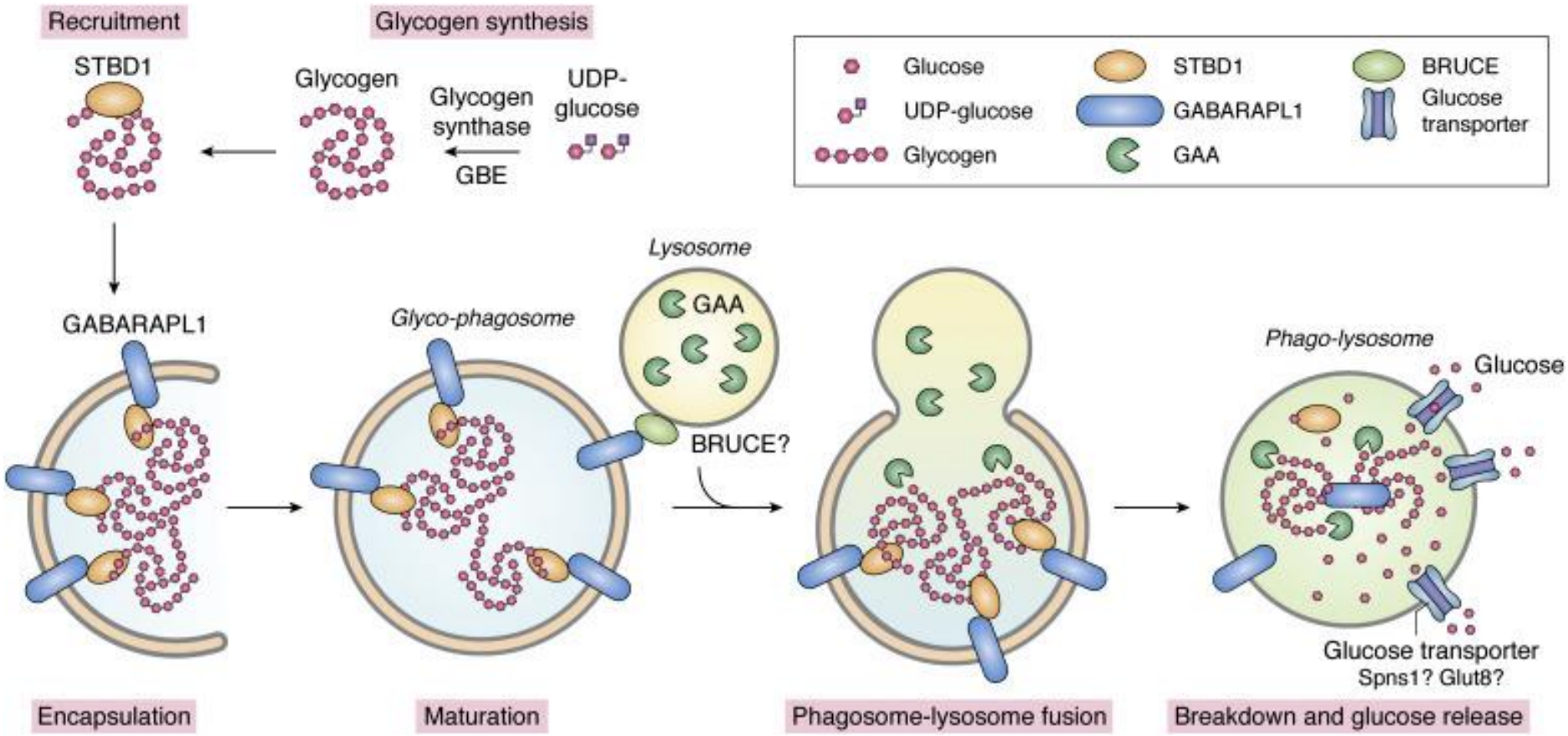


Table 1 A list of the classical glycogen storage diseases, Lafora disease and Danon disease depicting the enzyme/pathway involved and the Online Mendelian Inheritance in Man (OMIM) number.

Type	Alternate names or subtype	Affected enzyme/pathway	Gene	OMIM* phenotype no.
0	0a	Liver glycogen synthase	*GYS2*	240600
	0b	Muscle glycogen synthase	*GYS1*	611556
I	Ia; von Gierke	Glucose-6-phosphatase α	*G6PC*	232200
	Ib; von Gierke	Glucose-6-phosphate transporter	*SLC37A4*	232220
II	Pompe	Acid α-glucosidase	*GAA*	232300
III	Cori/Forbes	Glycogen debranching enzyme	*AGL*	232400
IV	Andersen	Glycogen branching enzyme	*GBE1*	232500
V	McArdle	Muscle glycogen phosphorylase	*PYGM*	232600
VI	Hers	Liver glycogen phosphorylase	*PYGL*	232700
VII	Tarui	Muscle phosphofructose kinase	*PFKM*	232800
IX	IXa	Phosphorylase kinase (α2 subunit)	*PHKA2*	306000
	IXb	Phosphorylase kinase (β subunit)	*PHKB*	261750
	IXc	Phosphorylase kinase (γ subunit)	*PHKG2*	613027
	IXd	Phosphorylase kinase (α1 subunit)	*PHKA1*	300559
X	–	Muscle phosphoglycerate mutase	*PGAM2*	261670
XI#	Fanconi-Bickel	Glucose transporter 2	*SLC2A2*	227810
XII	–	Aldolase A	*ALDOA*	611881
XIII	–	β-Enolase	*ENO3*	612932
XV	–	Glycogenin-1	*GYG1*	603942
Danon disease		Lysosomal-associated membrane protein 2	*LAMP2*	300257
Lafora disease	2A	Laforin	*EPM2A*	254780
	2B	Malin	*NHLRC1*	254780

*OMIM (Online Mendelian Inheritance in Man); #in earlier sources, GSD type XI was associated with a deficiency in lactate dehydrogenase A (OMIM 612933).

Classical GSDs

- Cumulatively, the incidence of GSDs is rare (<1:20,000).

- Glycogen storage diseases, like most metabolic diseases, are inherited in an autosomal recessive (AR) way. The degree of consanguinity determines the AR inherited diseases in a given area or population – where the risk of mutation is high, which does not exclude de novo mutations.

- The GSD IXα and Danon disease are the only GSD types which are X-linked and inherited recessively.

Classical GSDs

GSD I

GSD III

GSD IX

GSD Type I

- GSD type I is the most common and one of the most severe GSDs.

- Type I glycogen storage disease occurs in approximately 1 in 100,000 births. The prevalence of GSDI in Ashkenazi Jews is approximately 1 in 20,000.

GSD Sub-type I

1. GSD Ia, due to lack of glucose 6-phosphatase catalytic activity (G6Pase)

[spans 12.5 kb on chromosome 17q21 consists of 5 exons]

2. GSD Ib is due to a defect in the SLC37A4 glucose 6-phosphate transporter (G6PT)

[spans 5.3 kb on chromosome 11q23 and consists of 9 exons]

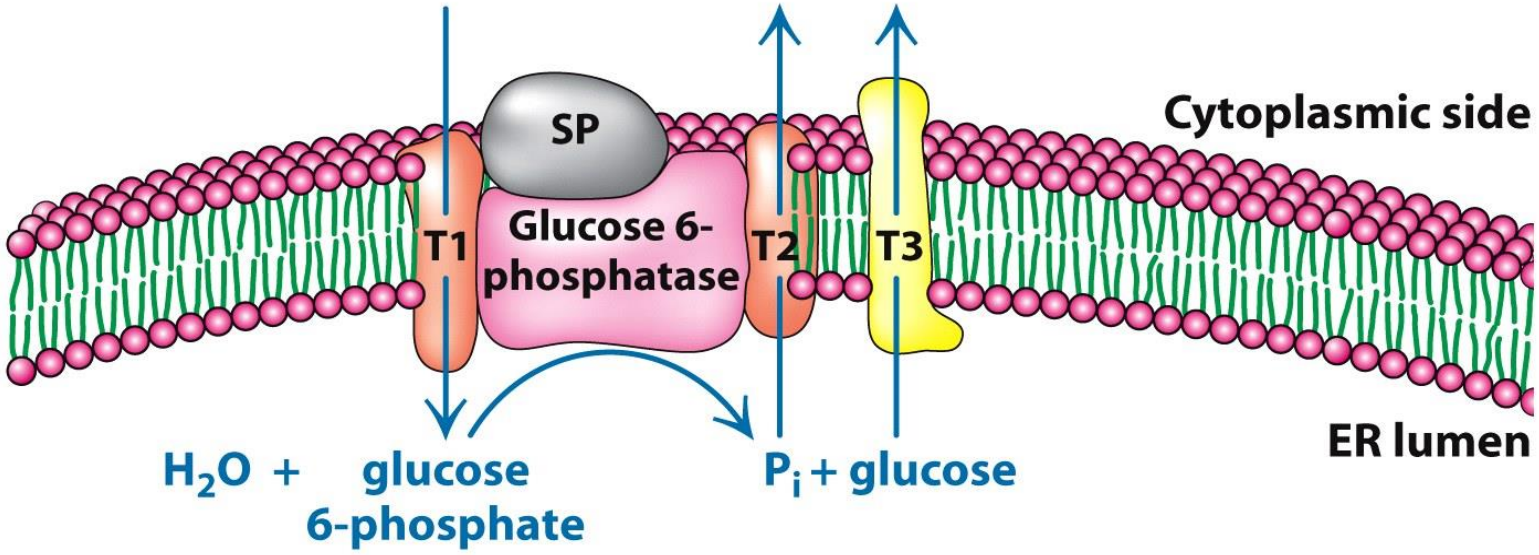


Figure 16.29
***Biochemistry*, Seventh Edition**

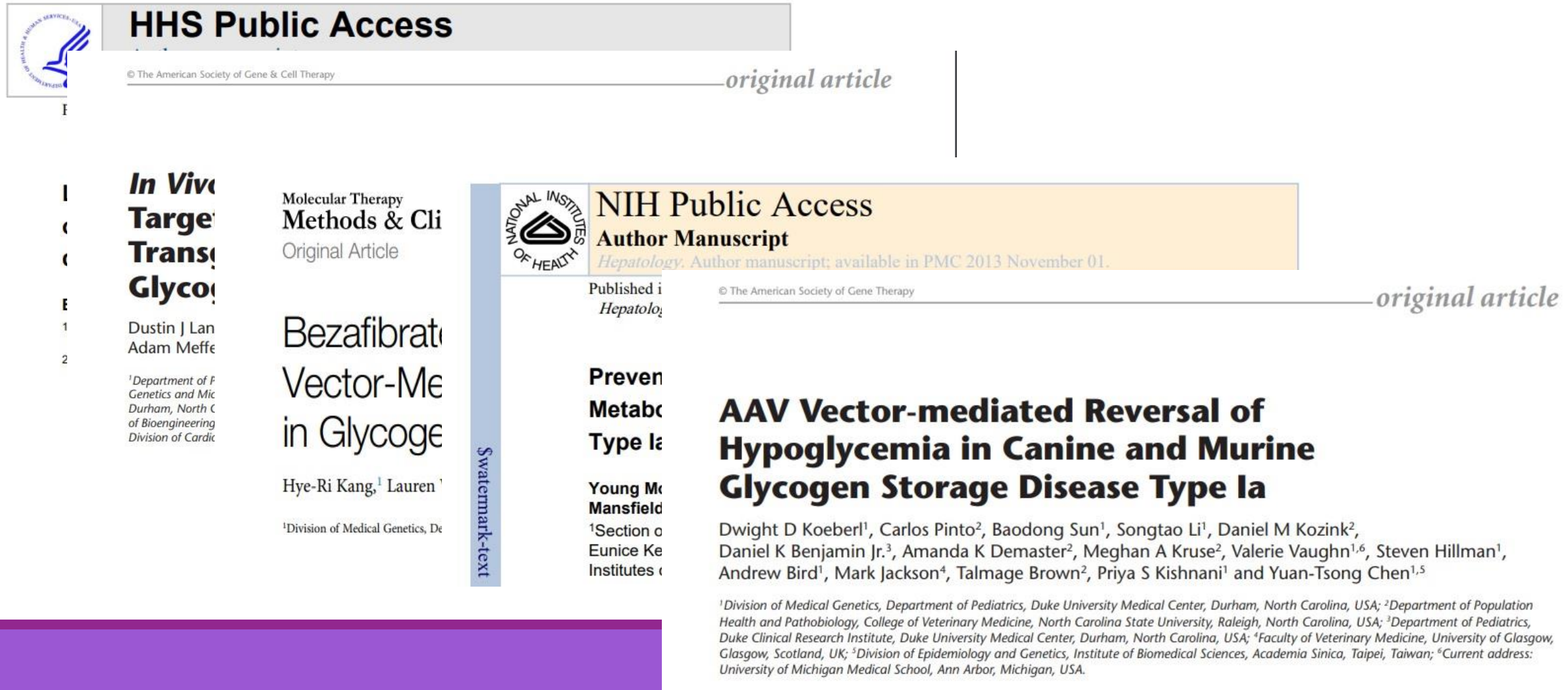
Common mutations in GSD Ia

cDNA change	Amino acid change	Ethnicity
c.247C>T	p.Arg83Cys	Caucasian (32%), Jewish (96%)
c.248G>A	p.Arg83His	Chinese (38%)
c.378_379dupTA	p.Tyr128Thrfs*3	Hispanic (50%)
c.648G>T	p.Leu216Leu; creates new splice site	Japanese (85–88%), Chinese (36–40%)
c.1039C>T	p.Gln347*	Caucasian (21%)

Common mutations in GSD Ib

cDNA change	Amino acid change	Ethnicity
c.352T>C	p.Trp118Arg	Japanese (37–50%)
c.1015G>T	p.Gly339Cys	Mixed Caucasian (19–21%), German (29%)
c.1042_1043delCT	p.Leu348Valfs*53	Mixed Caucasian (27–31%), German 32%

Gene Therapy for GSD Ia



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original article

AAV Vector-mediated Reversal of Hypoglycemia in Canine and Murine Glycogen Storage Disease Type Ia

Dwight D Koeberl[1], Carlos Pinto[2], Baodong Sun[1], Songtao Li[1], Daniel M Kozink[2], Daniel K Benjamin Jr.[3], Amanda K Demaster[2], Meghan A Kruse[2], Valerie Vaughn[1,6], Steven Hillman[1], Andrew Bird[1], Mark Jackson[4], Talmage Brown[2], Priya S Kishnani[1] and Yuan-Tsong Chen[1,5]

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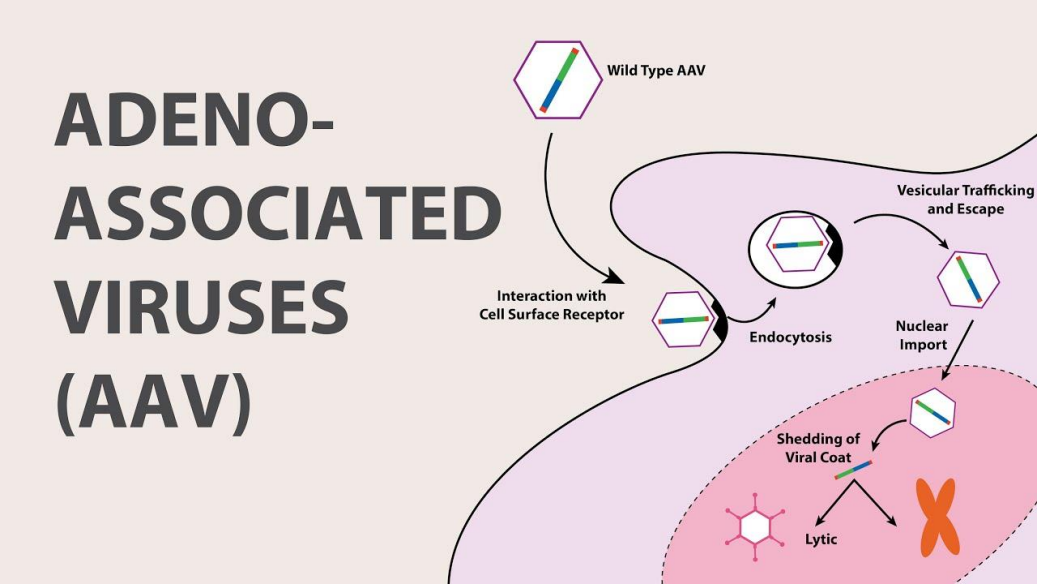
Gene Therapy for GSD Ia

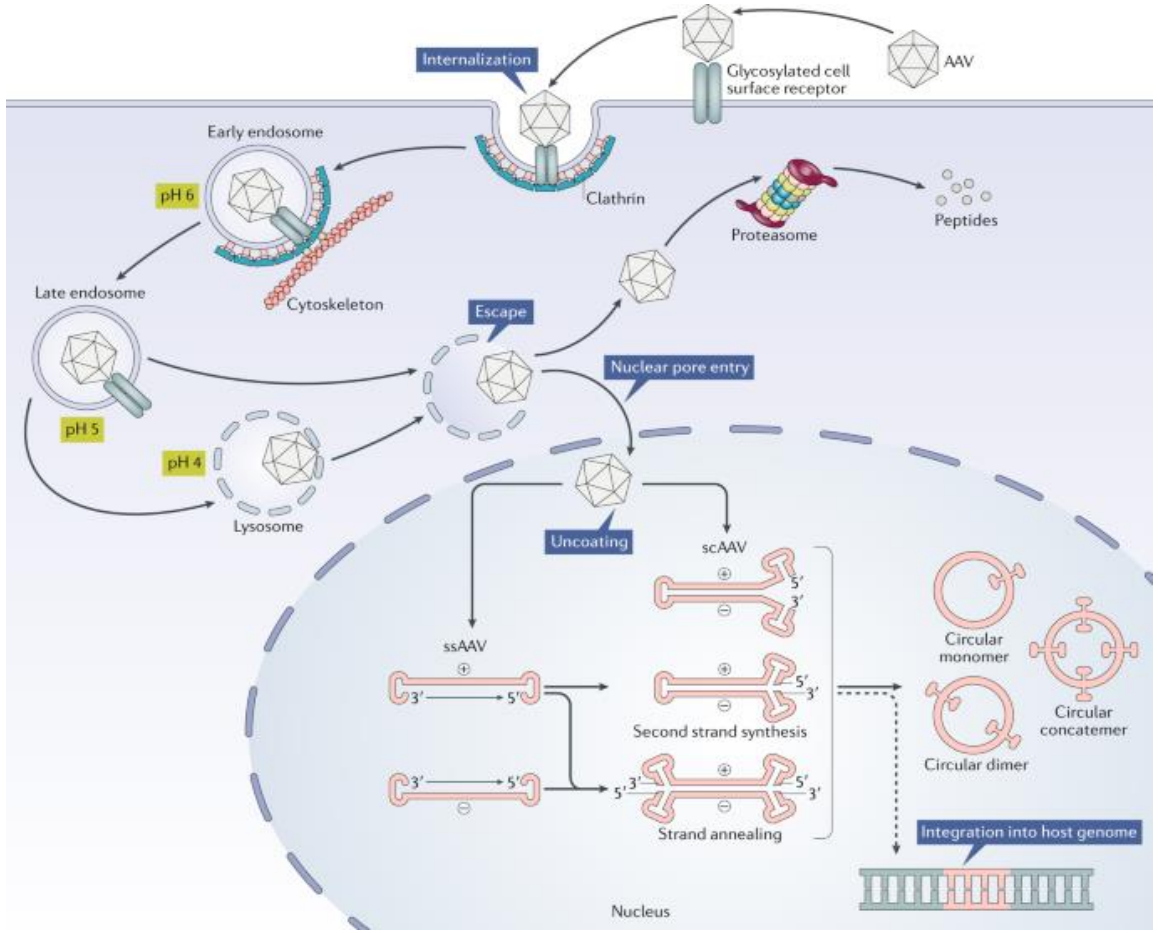
- Currently, in the USA, the development of adeno-associated virus (AAV) vector-mediated gene therapy is being carried out for GSD type Ia based on the success of early-stage clinical trials of gene therapy in hemophilia.



Gene Therapy for GSD Ia

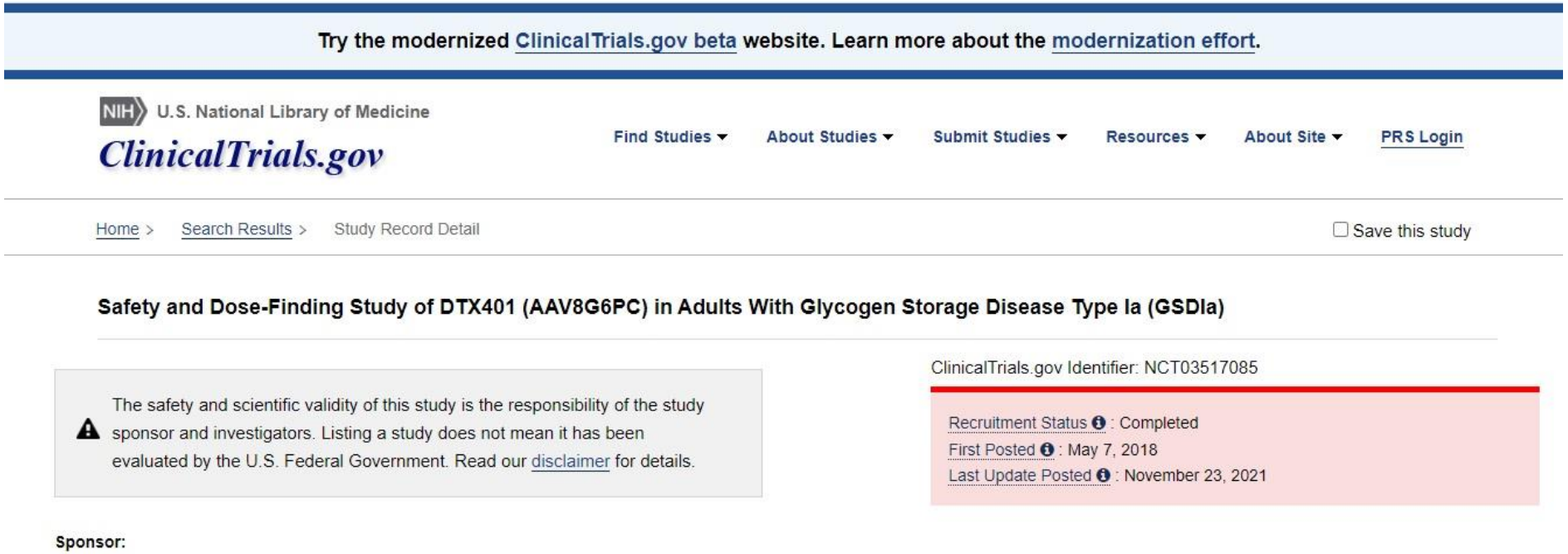
- AAV vectors containing a human G6Pase regulatory cassette/promoter have proven to be efficacious in animal models of GSD Ia, and these vectors contain sequence elements that regulate G6Pase expression appropriately.

rAAV8-co-G6PC Vector



Gene Therapy for GSD Ia

- At present, gene therapy for GSD type I is at the stage of a safety clinical trial on adult patients with this type of GSD, and is taking place in the Connecticut Hospital within the GSD program of Prof. Weinstein (NCT03517085).



Gene Therapy for GSD Ia

Arms and Interventions

Arm	Intervention/treatment
Experimental: DTX401 Dose 1 DTX401 solution for intravenous (IV) infusion	Genetic: DTX401 DTX401 administered as a single peripheral IV infusion Other Name: AAV8G6PC
Experimental: DTX401 Dose 2 DTX401 solution for intravenous (IV) infusion	Genetic: DTX401 DTX401 administered as a single peripheral IV infusion Other Name: AAV8G6PC
Experimental: DTX401 Dose 3 DTX401 solution for intravenous (IV) infusion	Genetic: DTX401 DTX401 administered as a single peripheral IV infusion Other Name: AAV8G6PC
Experimental: DTX401 Dose 4 DTX401 solution for intravenous (IV) infusion	Genetic: DTX401 DTX401 administered as a single peripheral IV infusion Other Name: AAV8G6PC

GSD III

- GSD III, also known as Cori Disease or Forbes disease, is caused by deficiency in the glycogen debrancher enzyme (GDE) resulting in impaired glycogen breakdown.

- GSD III is an autosomal recessive disease that has been reported in many different ethnic groups including Caucasians, Africans, Hispanics, and Asians.

- The frequency of the disease is approximately 1 in 100,000 births and relatively high in Sephardic Jews of North African extraction (prevalence 1:5400).

GSD III

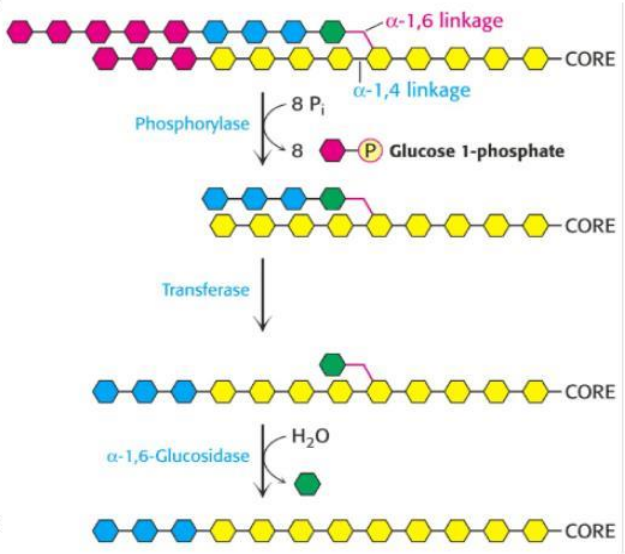
Glycogen Debranching Enzyme

The **glycogen debranching enzyme** (also called α-1,6-glucosidase) recognizes the partially degraded branch structure and remodels the substrate in a two step reaction.

1) the debranching enzyme transfers three glucose units to the nearest nonreducing end to generate a new substrate for glycogen phosphorylase.

2) the bifunctional debranching enzyme cleaves the α-1,6 glycosidic bond to release free glucose.

Since α-1,6 branch points occur *abou once every 10 glucose residues* in glycogen, complete degradation releases ~90% glucose-1P and 10% glucose molecules.



Is there a difference in the amount of energy that can be recovered from glucose-1P and glucose?

- This disorder is divided into four subtypes:

1. GSD IIIa (Liver and Muscle)
2. GSD IIIb (Liver)
3. GSD IIIc (Muscle)
4. GSD IIId (Liver and Muscle)

Mutations GSD III

-Glycogen storage disease III (GSD III) is caused by homozygous or compound heterozygous mutation in the AGL gene, which encodes the glycogen debrancher enzyme, on chromosome 1p21 consisting of 35 exons.

- GSD IIIa: In the United States, **p.R864X (10.3%), c.3964delT (6.7%), c.4260-12GA (IVS32-12AG) (5.5%), and p.R1228X (5.2%)** are the most common mutations but together account for only 28% of all mutant alleles.

- Unlike GSD IIIa, which is associated with allelic heterogeneity, two mutations in exon **3—c.18_19delGA (p.Gln6HisfsX20),** and **c.16CT (p.Gln6X)**—are specifically associated with the GSD IIIb phenotype.

GSD TYPE IX

- The GSD type IX consists of a lack of phosphorylase kinase (PhK) enzyme, which plays a role in the process of glycogen degradation.

- The enzyme occurs in many tissues, thus its subunits also have their specific isoforms. The activity of PhK has been studied in such organs as the liver, muscles, kidney, testes, heart and also in erythrocytes, leukocytes and nerve cells.

Phosphorylase kinase (PhK) subunit genes known to cause PhK deficiency

Gene	Sub-type of GSD	PhK subunit	Location	Inheritance	Tissue/organ primarily affected
PHKA1	IXa	α	Xq13.1	X-linked	Muscle
PHKA2	IXa	α	Xp22.13	X-linked	Liver
PHKB	IXb	β	16q12.1	Autosomal recessive	Liver
PHKG2	IXc	γ	16p11.2	Autosomal recessive	Liver

GSD TYPE IX

Benign or not benign? Deep phenotyping of liver Glycogen Storage Disease IX

GSD TYPE IX

GSD IX is one of the most common forms of glycogen storage disease, accounting for about 25% of cases.

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Clinical and genetic spectrum of glycogen storage disease in Iranian population using targeted gene sequencing

Zahra Beyzaei[1], Fatih Ezgu[2], Bita Geramizadeh[1,3]✉, Mohammad Hadi Imanieh[4], Mahmood Haghighat[4], Seyed Mohsen Dehghani[4], Naser Honar[4], Mojgan Zahmatkeshan[4,5], Amirreza Jassbi[6], Marjan Mahboubifar[6] & Alireza Alborzi[7]

Glycogen storage diseases (GSDs) are known as complex disorders with overlapping manifestations. These features also preclude a specific clinical diagnosis, requiring more accurate paraclinical tests. To evaluate the patients with particular diagnosis features characterizing GSD, an observational retrospective case study was designed by performing a targeted gene sequencing (TGS) for accurate

GSD TYPE IX

ACMG PRACTICE RESOURCE | Genetics inMedicine

Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

A full list of authors and affiliations appears at the end of the paper.

Disclaimer This practice resource is designed primarily as an educational resource for medical geneticists and other clinicians to help them provide quality medical services. Adherence to this practice resource is completely voluntary and does not necessarily assure a successful medical outcome. This practice resource should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen.

Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this practice resource. Clinicians also are advised to take notice of the date this practice resource was adopted, and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

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